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REDACTED VERSION

VIA ECF
Honorable Julien Xavier Neals
U.S. District Court for the District of New Jersey
Martin Luther King Jr. Building & U.S. Courthouse
50 Walnut Street
Newark, New Jersey 07102

Re: *Corcept Therapeutics, Inc. v. Teva Pharmaceuticals USA, Inc.*
Civil Action No.: 2:18-cv-3632-JXN-LDW (Consolidated)

Dear Judge Neals:

This firm, along with Sterne, Kessler, Goldstein & Fox PLLC, represents Defendant Teva Pharmaceuticals USA, Inc. in this case. Pursuant to L. Civ. R. 7.1(d)(3) and (6), Teva respectfully requests leave to submit the following brief reply in support of its cross-motion for summary judgment of non-infringement of the '214 patent in order to (i) correct certain misstatements of law and fact in Corcept's opposition to Teva's cross-motion and (ii) respond to certain new arguments raised by Corcept.

I. Introduction

The undisputed language of Teva's proposed label resolves this case. Nothing in Teva's label encourages, recommends, or requires a critical step of the claimed method: administration of a strong CYP3A inhibitor to a patient already taking mifepristone. Corcept's attempts to show otherwise all rest on different versions of the same illogical argument: because (Corcept says) Teva's label instructs physicians that, *if* they decide to co-administer mifepristone and a strong CYP3A inhibitor, they should reduce the mifepristone dose in a manner that could infringe, Teva can be held liable for infringement. The Federal Circuit considered and rejected that exact argument in *HZNP Medicines LLC v. Actavis Laboratories UT, Inc.*, 940 F.3d 680, 702–03 (Fed. Cir. 2019). And it did so for sound reasons: an instruction to do Y *if* one does X is not, as a matter of law or logic, an instruction to do X. Accordingly, Teva respectfully submits that it cross-motion for summary judgment of non-infringement should be granted.

II. Teva's label does not encourage, recommend, or promote co-administration of mifepristone and strong CYP3A inhibitors.

Contrary to Corcept's repeated assertions (at 1, 4, 8, 10, 18, 20, 23), Teva's label does *not* instruct that co-administration of mifepristone and strong CYP3A inhibitors is ever "necessary" or "required." Teva's label tells physicians that, *if they decide* to administer a strong CYP3A inhibitor to a Cushing's patient who is already taking mifepristone, *then* they should reduce the dose of mifepristone. Ex. U § 2.5. This information does not encourage anyone to do anything in

the first instance. The label is silent on whether co-administration should even be considered (much less actually undertaken), and it contains no guidance on when concomitant use would be sensible, let alone "necessary." It could hardly be otherwise, of course. Teva is seeking approval to market mifepristone for the treatment of Cushing's syndrome; Teva is *not* seeking approval to market any strong CYP3A inhibitor (for the treatment of Cushing's syndrome or any other condition). And Teva's label legally cannot instruct a use for which Teva is not seeking approval. *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1322–23 (Fed. Cir. 2012) (FDA regulations do not permit generic pharmaceutical companies to imply or suggest that their product has indications or uses other than those approved by the FDA). If anything, the label cautions *against* the combination of mifepristone and strong CYP3A inhibitors because of the potential drug-drug interaction that could result. Teva Br. 8–11; Ex. U § 2.5.

Binding Federal Circuit precedent—*HZNP* in particular—holds that there can be no inducement under these circumstances. Teva Br. 11–19. "In ANDA cases, when a plaintiff attempts to draw intent from the label," the label must "encourage[], recommend[], or promote[] infringement"; "[m]erely describing the infringing use, or knowing of the possibility of infringement, will not suffice." *HZNP*, 940 F.3d at 701–03. Teva's label here at most describes—but does not encourage—an infringing use. Teva therefore is not liable for infringement.

More specifically, the lesson of *HZNP*, as explained above and in Teva's opening brief (at 11–13), is that a label stating, "If you do X, then do Y" is *not* an instruction to do X. That principle is directly applicable here. Corcept never engages with this fundamental point. Instead, it repeatedly contends (e.g., at 23) that Teva can be held liable for inducement because the Y step is "required" *if the physician does X*. As *HZNP* makes clear, that is not the law.

Corcept's assertion (at 4) that Teva's argument is "fabricated" is illogical. Teva's argument is a direct application of *HZNP*'s holding: "The warning, then, operates in an 'if/then' manner: *if* the user wants to cover the treated area with clothing or apply another substance over it, *then* the patient should wait until the area is dry. This does not encourage infringement . . . ." *HZNP*, 940 F.3d at 702. The label's instructions here work the same way: *if* the physician wants to co-administer mifepristone and strong CYP3A inhibitors, *then* she should follow the dose-titration instructions in section 2.5. "This does not encourage infringement." *Id.*

Moreover, contrary to Corcept's straw-man contention (at 6), *HZNP* does not "preclude any future finding of induced infringement for *any* method of treatment." As Teva's opening brief explained (at 14), "the question for inducement purposes is whether the label—*assuming the physician chooses to follow it*—requires each step of the patented method." The answer was no in *HZNP*, because the label did not encourage or require the application of a second substance. And the answer is no here, because Teva's label does not encourage or require co-administering mifepristone and strong CYP3A inhibitors. A physician may follow the label repeatedly—as Corcept's own expert has, Teva Br. 9–10—and yet *never* choose to administer a strong CYP3A inhibitor along with mifepristone.[1]

[1] Corcept's assertion (at 10–11) that "Teva argues that 100% of a drug's use according to its package insert must infringe for there to be induced infringement" represents a similar (and similarly misguided) attempt at a straw man. That is *not* Teva's position. Teva's argument is simply that inducement requires the label to *encourage*—as opposed to merely *permit*—at least some users to infringe. *See, e.g.*, *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1055 (Fed. Cir. 2010) (affirming finding of inducement because label instructions "would necessarily lead" some

In the cases relied upon by Corcept, in contrast, following the label instructions *did* inevitably lead to at least some instances of infringement. *Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd.*, 887 F.3d 1117 (Fed. Cir. 2018)—which Corcept repeatedly invokes—is an excellent example.

The label instructions in *Vanda* led directly to the claimed method: the label recommended administering 12 mg/day iloperidone or less to poor-metabolizer schizophrenia patients and 12–24 mg/day iloperidone to non-poor-metabolizer schizophrenia patients. *Id.* at 1122. Those dosing instructions were *precisely* what the patent claimed. *Id.* at 1121. And, while the label did not require "ever administering the drug to a poor CYP2D6 metabolizer," Corcept Reply 9–10, administration of the drug to a non-poor CYP2D6 metabolizer according to the label *infringed the patent too. See Vanda*, 887 F.3d at 1121 (claim language required "administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day" "if the patient does not have a CYP2D6 poor metabolizer genotype"). Corcept's contention (at 10–11) that administration to a non-poor metabolizer did not infringe the patent in *Vanda* is simply false.

Corcept's attempt to analogize this case to *Vanda* thus rests on a mischaracterization of that case. In *Vanda*, a physician administering iloperidone—to *either* a poor *or* non-poor metabolizer—according to the dosing instructions in the label would *always* infringe. Here, in contrast physicians administering mifepristone according to the dosing instructions in the label will *never* infringe, unless they also do something the label nowhere recommends—namely, also administering a strong CYP3A inhibitor to a patient already taking 900 mg mifepristone.

Notably, *HZNP* itself rejected an identical argument to the one Corcept advances here. HZNP argued that Actavis could be held liable for inducement because Actavis's label instructed that patients should avoid exposure to "sunlight on the treated knees" and therefore that "application of sunscreen is medically necessary." 940 F.3d at 701; *see also id.* ("Although Horizon recognizes that not every user will need to apply sunscreen, insect repellant, or another topical medication, it contends that, when such need arises, Actavis's instruction will lead to an infringing use."). But, as the Court explained, Horizon's conclusion did not follow from its premise:

> The warning, then, operates in an "if/then" manner: *if* the user wants to cover the treated area with clothing or apply another substance over it, *then* the patient should wait until the area is dry. *This does not encourage infringement, particularly where the label does not require subsequent application of sunscreen, insect repellant, or a second medication.*

Id. at 702 (third emphasis added).

The same is true here. Even if Corcept had established that co-administration of mifepristone and strong CYP3A inhibitors would ever be "medically necessary"—and Corcept has failed even to do that—it would be irrelevant because Teva's label nowhere encourages that co-administration. If co-administration occurs, it will be solely because a physician, based on her independent medical judgment, deems it necessary—just as, in *HZNP*, if a second topical

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patients—those "whose previous treatments fell within the first two rows of the dosage table"—to infringe). The label here does not meet that standard.

medication were applied, it was solely because the patient or her physician deemed it necessary. There can be no inducement in such circumstances.

Judge Simandle's opinion in *Otsuka Pharmaceutical Co. v. Torrent Pharmaceuticals Ltd., Inc.*, 99 F. Supp. 3d 461 (D.N.J. 2015), likewise illustrates why Corcept's argument is wrong. Corcept's argument essentially proceeds as follows: (i) Teva's label acknowledges that it could be "necessary" to co-administer mifepristone and a strong CYP3A inhibitor; (ii) there are certain circumstances in which physicians might find it necessary to attempt such co-administration, *see* Corcept Op. Br. 2–6; and so (iii) Teva intends for physicians to co-administer when those circumstances are present. The *Otsuka* court confronted and rejected a similar argument. There, the patent required the administration of aripiprazole (the ANDA product) with citalopram or escitalopram (two other antidepressants), and the *Otsuka* label disclosed studies that reported a decreased risk of suicidality associated with the claimed use in a certain population. 99 F. Supp. 3d at 494. The plaintiff argued that the inclusion of these studies would have induced physicians to co-administer aripiprazole and citalopram or escitalopram, but the court disagreed.

The label language, the court explained, "convey[ed], at most, indifference to the administration of the ANDA products in conjunction with [citalopram or escitalopram], and impl[ied] that aripiprazole *could* be administered with" those drugs. *Id.* But that was not sufficient to show inducement. *Id.* The generic label, the court reasoned, "must necessarily" include safety information describing an infringing use because "the primary market to which these generic aripiprazole products may be prescribed" includes patients "who may happen to be taking" citalopram or escitalopram, and "[d]efendants cannot prevent their [ANDA] products from being prescribed in connection with [citalopram or escitalopram]." *Id.*; *see also id.* at 484 ("The relevant inquiry for purposes of inducement is not, however, 'whether a user following the instructions may end up using the device in an infringing way.'") (quoting *Vita–Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009)).

Teva's label, like the *Otsuka* label, "specifically warn[s]" healthcare providers "of the potential pitfalls and risks of" concomitant use, and stops short of prescribing a specific course of action, *id.* at 494. And like the *Otsuka* label, Teva's label includes safety information describing an infringing use because the primary market includes physicians that might find it necessary to administer mifepristone along with a strong CYP3A inhibitor. *See* Corcept Op. Br. 2–6. But this safety information "convey[s] little more than the knowledge of possible infringement, not the specific intent and action to induce required for infringement." *Otsuka*, 99 F. Supp. 3d. at 494.

III. Corcept's attempts to avoid *HZNP* lack merit.

Corcept's attempted distinctions of *HZNP* (at 8, 18) fail at every turn.

Corcept's first and third purported distinctions (at 8) rest on the premise that Teva's label, in contrast to the label at issue in *HZNP*, instructs that the patented method is "necessary" and "required." As explained above, that premise is wrong. Teva's label *does not say that*. On the contrary, it recommends *against* co-administration if it can be avoided. It is only "*if*" the physician, in her own medical judgment, deems co-administration necessary that certain additional steps should be taken. Ex. U § 2.5; Ex. 3 (Carroll) 133:8–10 ("if there's no indication to use a strong CYP3A inhibitor, then a strong CYP3A inhibitor is not administered").

Corcept's second attempted distinction of *HZNP* (at 8)—that the label there was "broader than [the] claimed method"—also fails. The label here provides for administration of 300–1200

mg mifepristone to control hyperglycemia secondary to hypercortisolism in certain patients, whereas the claims are narrowly limited to the administration of certain specified strong CYP3A inhibitors to a patient already receiving 900 mg or 1200 mg mifepristone. Even the label's cautionary instructions are broader than the asserted claims: these warnings apply to co-administration of *any* mifepristone dose with *any* strong CYP3A inhibitor (not just those specified in the claims), irrespective of the order the agents are administered. So here, just as in *HZNP*, the label is broader than the claims.

Finally, Corcept's suggestions (at 8, 18–19) that the instructions in *HZNP* were not premised on safety concerns are flatly incorrect. The *HZNP* label's warnings were included so patients would avoid potential adverse reactions that were known to result if the treated area were exposed to sun or if a second topical composition were applied before waiting for the diclofenac composition to dry. *See HZNP*, 940 F.3d at 701 & n.11. But the warnings were just that—warnings about what to do *if* the patient found it necessary to apply a second topical composition (like sunscreen, for example). They were not instructions to apply a second topical composition in the first place. Similarly, here, the warnings in Teva's label are included to avoid the potential adverse drug-drug interaction that can result in co-administering mifepristone and strong CYP3A inhibitors. But the warnings are just that—warnings about what to do *if* the two drugs are co-administered. They are not instructions to physicians to actually co-administer in the first place.

Perhaps recognizing that any reasonable reading of *HZNP* is fatal to its case, Corcept alternatively suggests (at 5–6) that *HZNP* is not good law. That is wrong, of course. *HZNP* simply followed well-settled precedent requiring that a generic label "encourage, recommend, or promote infringement" in order to create liability for inducement and holding that "[m]erely describing the infringing use . . . will not suffice." *HZNP*, 940 F.3d at 702 (quoting *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015)). More to the point, however, if Corcept wishes to argue that *HZNP* was wrongly decided, that is an argument for the Federal Circuit, not this Court. *HZNP* is, by a long shot, the most factually on-point Federal Circuit case—and it is binding precedent, however much Corcept may wish that were not so.

HZNP, in short, is directly on point. And it compels a finding of non-infringement.

IV. Corcept's remaining arguments lack merit.

Corcept's attempts (at 12–13) to rewrite the prosecution history also fail. Corcept's statements during prosecution speak for themselves: Corcept argued that the 2012 Korlym Label taught "those of skill in the art . . . to *avoid use of mifepristone with CYP3A inhibitors*" and "*contraindicated*" the combination. Ex. 4 at CORMIFE-T-00002182 (emphases added). Indeed, even now, Corcept characterizes (at 13) the 2012 label's recommendation to use "extreme caution" when co-administering as a "warning" (even though that label, like the current one, permitted the combination if the physician deemed it "necessary"). Corcept's contention that the new label somehow *encourages* the combination because the new label recommends "caution" instead of "*extreme caution*," Corcept Reply 13, is not credible. And the various label versions' consistent cautionary instructions explain quite well why neither Corcept's expert Dr. Carroll nor Teva's expert Dr. Snyder—both experienced endocrinologists—has ever actually attempted the combination.[2]

[2] The fact that Corcept can point (at 15) to evidence that co-administration has happened at some point in the past is irrelevant, both because the existence of direct infringement is insufficient to

Nor does Table 3 of the label, upon which Corcept heavily relies (at 17–21), aid Corcept's case. As Corcept admits (at 17), Table 3 "contains clinical trial data indicating how much mifepristone blood serum concentrations will rise as a result of co-administration with strong CYP3A inhibitors." These trials were drug-drug interaction studies in *healthy subjects*. Ex. U § 12.3. Their results indicate the extent of the pharmacokinetic interaction between mifepristone and strong CYP3A inhibitors. *Id.* But the results say nothing about whether co-administration of the two drugs is necessary, or even beneficial, *in the treatment of Cushing's syndrome* (or any other condition). And they do not encourage using the combination to treat Cushing's patients.

Moreover, Corcept's claim (at 8–9) that the inclusion of this clinical data indicates that "the claimed methods are safe" is misleading. Teva's proposed label advises caution when co-administering mifepristone and strong CYP3A inhibitors and includes warnings that discourage the combination because *safety concerns remain* despite the presence of the clinical data and the dose adjustment procedures. Ex. U §§ 5.6, 7.2; *see also* Ex. Y (Hamrahian) at 191:3–13 ("Every patient on mifepristone," regardless of dose, "should be watched for adrenal insufficiency"); *id.* at 194:9–10 ("Hypokalemia is a common adverse event in patients with Cushing's syndrome"); *id.* at 107:1–4 (testifying that hypokalemia and adrenal insufficiency can be fatal). Corcept's actual point appears to be that, in light of the clinical data, physicians may sometimes decide that the potential benefits of co-administering mifepristone and strong CYP3A inhibitors outweigh the risks. *See* Ex. 3 (Carroll) 128:20–130:15 (stating that concomitant administration is "safe" if the "benefits are likely to outweigh the risks"). But all that shows is that the label *permits* infringement. Mere permission is categorically insufficient to show inducement. *HZNP*, 940 F.3d at 702; *see Otsuka*, 99 F. Supp. 3d at 490 (courts have "consistently rejected safety discussions as a basis for inducement liability"); *id.* at 494 (rejecting argument that precautionary instructions could result in inducement liability, even though following precautions could result in infringement, because inclusion of those instructions "convey[ed] little more than the knowledge of possible infringement").[3]

Corcept's position is essentially that Teva should be liable for inducement because its label permits concomitant use without *forbidding* the patented method. But that argument "turns the legal test on its head. [Corcept] needs to show that [Teva] took affirmative steps to induce, not affirmative steps to make sure others avoid infringement." *Takeda*, 785 F.3d at 631 n.4; *see also Otsuka*, 99 F. Supp. 3d at 493 ("'[P]ermitting an infringing' use differs, in significant respects,

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show inducement and because the claims require more than simply co-administering the two drugs. There is *no* evidence—none—of any physician ever actually having practiced the *steps of the claimed method*.

[3] Contrary to Corcept's suggestion (at 24), the fact that *Otsuka* involved a carve-out does not somehow render its discussion of inducement law inapplicable here. On the contrary, Otsuka's argument was that the safety information that was *not* carved out of the label induced infringement, and the court rejected that argument because "'[a] warning provides information regarding a potential risk,' but stops short of prescribing a specific 'course of action.'" *Otsuka*, 99 F. Supp. 3d at 493 (quoting *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, at *18 (D.N.J. Aug. 29, 2014)). Relatedly, Corcept's contentions (at 21–27) that [redacted] are beside the point. [redacted] because the label does not encourage (as opposed to merely permit) anyone to co-administer mifepristone and strong CYP3A inhibitors in the first place. Teva Br. 23–25.

'from encouragement.'") (quoting *Shire LLC v. Amneal Pharm., LLC*, 2014 WL 2861430, at *5 (D.N.J. June 23, 2014)).

Corcept's reliance (at 9–10) on *Vanda*, *Sanofi*, and *Amarin* for the proposition that clinical data included in a drug label can be evidence of specific intent to infringe is misplaced. As to *Vanda*, Corcept incorrectly suggests (at 9) that the *Vanda* Court found "pharmacokinetic data" to "'constitute[] a recommendation' to perform the claimed methods." That is *not* what *Vanda* said—not even close. The Federal Circuit concluded that the *Vanda* label's instructions that (i) poor CYP2D6 metabolizers "should have their dose [of iloperidone] reduced by one-half" and (ii) genotyping tests were "available to identify" those poor metabolizers of CYP2D6 "constitute[d] a recommendation to perform genotyping tests." 887 F.3d at 1131. Nothing in Table 3 (or anywhere else in Teva's label) contains similar instructions recommending the patented method.

Sanofi holds that the existence of substantial non-infringing uses does not preclude a finding of inducement. *Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017). And, in finding inducement in that case, the Federal Circuit (i) highlighted specific language in the ANDA label promoting the benefits of infringing uses and discouraging non-infringing uses and (ii) credited expert testimony that (a) approximately 77% of the branded drug's prescriptions were for infringing uses and (b) healthcare providers were particularly "reluctan[t]" to use the drug in a non-infringing manner. *Id.* at 645. This case could not be more different. Corcept has presented no evidence of *any* instance of an infringing use; Teva's proposed label warns *against* co-administration of mifepristone and strong CYP3A inhibitors; and the clinical data in the label (which, again, are pharmacokinetic data from healthy subjects) provides no information about whether the claimed methods are even beneficial—much less necessary—for the desired patient population.

Finally, in *Amarin*, the district court's inducement holding rested on findings that (i) "the indication and usage section of the proposed labels" "suggest[ed] that the applicable drugs will be prescribed" in an infringing manner; (ii) the alleged non-infringing uses "in most cases" would *harm* the patient; (iii) the prescribing practices of both side's experts were generally infringing; and (iv) there was "no real dispute" that most prescriptions would result in an infringing use. *Amarin Pharma, Inc. v. Hikma Pharm. USA Inc.*, 449 F. Supp. 3d 967, 999, 1001 (D. Nev. 2020). None of those facts is present here. Again, *there is no evidence of anyone ever having infringed this patent*. If Corcept were correct that the label actually encourages physicians to infringe, then surely Corcept could have provided some evidence of a physician who actually had done so. But Corcept has not. That failure speaks volumes.

V. Conclusion

Simply put, the basis for Corcept's attempting to prolong its decade-long mifepristone monopoly is a patent on a method that Teva's label does not encourage and that, as far as the evidence in this case shows, no one has ever actually performed. As such, Teva respectfully submits that the Court should grant summary judgment of non-infringement.[4]

[4] Corcept's assertion (at 2 n.1) that Teva is estopped from contesting the PTAB's factual conclusions in the parallel post-grant review is irrelevant to infringement, but Teva notes for the record that it is also wrong on the law. PGR estoppel applies to *invalidity grounds*, not individual facts. *See* 35 U.S.C. § 325(e)(2) (PGR petitioner may not argue that a "claim is invalid on any ground that the petitioner raised or reasonably could have raised" in the PGR).

Respectfully submitted,

s/Liza M. Walsh

Liza M. Walsh

cc: All Counsel of Record (via ECF and Email)